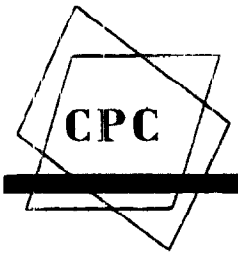

COMBINATION PRODUCT COALITION

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Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
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Rockville, MD 20852

RE: Response to Request for Comment on Primary Mode of Action, Food and Drug Administration Docket Number 2004N-0194

Dear Sir or Madam:

The Combination Products Coalition ("CPC") respectfully submits these comments in response to the Food and Drug Administration's ("FDA") Proposed Rule and Request for Comment on the "Definition of Primary Mode of Action of a Combination Product." The CPC is a group of leading pharmaceutical, biologics and medical device manufacturers with substantial experience in the combination products arena, as well as in each of the constituent technologies. Because of its diverse membership, the CPC brings a uniquely broad, combination product perspective to the regulation of such products. With that in mind, we offer the following comments.

I. General Comments

The CPC applauds the FDA's effort in crafting this Proposed Rule, and believes the FDA did a remarkable job in listening to the comments on mode of action and primary mode of action expressed by stakeholders in prior hearings. As a result, the overall architecture of the Proposed Rule has a solid foundation. Nonetheless, we believe that certain improvements could be made to better ensure that the rule ultimately adopted by the FDA accommodates the tremendous diversity in combination products, as well as the novel issues that innovative combination products raise. To that end, we offer the following specific comments.

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II. Specific Comments

A. Mode of Action

The CPC agrees generally with FDA's definition of "mode of action" in proposed 21 CFR § 3.2, as "the means by which a product achieves a therapeutic effect." In addition, the CPC agrees that, when making assignments of combination products, the agency should consider each of the modes of action contributed by the constituent parts of a combination product. We have some concern, however, with the specific language provided in the Proposed Rules' definitions, and with how that language will be interpreted once the rule is implemented. We offer the following specific thoughts:

1. The definition of biological mode of action should be revised.

The CPC is concerned that the definition of a "biological product mode of action" is incomplete and impractical to implement. The definition fails to include important cellular products, particularly non-blood cellular products like certain therapeutic stem cells that historically have been treated as biologics. Consider the following examples:

- Under this definition of mechanism of action, an extracorporeal blood treatment consisting of liver cells on a matrix would not be considered as having a biological mode of action.
- Likewise, a combination product with a neural stem cell component would fall outside that mode of action.
- Vectors used in gene therapy that are derived from biological entities other than viruses also would not be included within the definition.

In addition, the definition merely includes a list of product types, rather than a true "mechanism of action." While we understand that the terminology provided in the definition tracks the description of a biological product contained in 42 U.S.C. § 262(i), that terminology is merely a description, and not an operational definition. For that reason, we recommend that FDA adopt a definition that can be more easily implemented in practice, such as the following:

> A constituent part has a biological product mode of action if it entails intact cell function or replication (including tissues), genetic modification in the host, an immune response, and/or it acts by means of blood, a blood component, or blood derivative.

This definition alleviates the problems inherent in the language currently supplied in the Proposed Rule. In addition, it covers innovative new products not included in the proposed list, but treated as biologics -- including therapeutic stem cell products not derived from blood. It also allows room for innovation. Unlike the proposed descriptive list that considers known product types, the definition provided above considers only the mechanism of action. As medical technology advances into currently unknown realms, this definition should be flexible enough to endure.

We believe that the notion of "mode of action" is critical to the intelligibility of the Proposed Rule, and that additional effort spent refining the definition would therefore benefit all stakeholders. For that reason, we welcome and encourage further discussion regarding this proposed definition of biological mode of action.

2. The Proposed Rule should clarify treatment of virtual combination products and kits.

Although FDA has declared that (1) separate products packaged together as "kits" and (2) products not packaged as a unit but required to be used together to achieve the intended use, indication or effect ("virtual combination products") are combination products,[1] FDA does not specifically address such products in the Proposed Rule. In fact, the examples provided in the Proposed Rule are limited to "integral" combination products -- those combination products that are "physically, chemically, or otherwise combined or mixed and produced as a single entity."[2] For the reasons explained below, we believe the FDA should more fully address kits and virtual combination products in the Proposed Rule.

a) The current process has flexibility, but lacks consistency and predictability

At this point, FDA's handling of kits and virtual combination products varies, depending in large part on the approach a manufacturer takes in submitting the application or applications. Other than some very general guidance in the Inter-Center Agreements, FDA has no specific guidance or requirements regarding how these combination products are to be treated for designation purposes, so manufacturer's often decide for themselves how to proceed. As you might guess, we think that aspect works well. If separate applications are submitted, they typically are reviewed separately. If a combined application is submitted, a lead agency component is designated, and the review proceeds accordingly.

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[1] *See* 21 CFR § 3.2(e).

[2] *See* 21 CFR 3.2(e) (defining combination product).

However, sometimes the process does go awry. Without directional guidance from OCP, agency components may respond in inconsistent and sometimes unpredictable ways. For instance:

- One manufacturer sought to add the name of a 510(k)-cleared reusable drug delivery system to its drug label. The Center for Drug Evaluation and Research ("CDER") believed that adding information about the cleared device to the approved drug label required their approval. Consequently, CDER reviewed device performance data for the drug delivery device, treating the review under the timeframes and guidelines for drug review. CDER appeared to treat the device in combination with the drug, despite treating them previously as separate entities.

- With certain "convenience kits," the agency exercises its enforcement discretion and does not require 510(k) clearance. As long as a manufacturer or assembler can reasonably conclude that further processing of a "convenience kit" and its components does not significantly affect the safety or effectiveness of any of its components, and has documentation to support that determination, 510(k) clearance is not required. Without filings to support the product, the rules for making modifications and other downstream issues is unclear and needs additional guidance. For instance, while FDA would allocate to CDER responsibility for determining premarket requirements of a drug component added to the kit, it is not clear what status the kit itself would take on following such a modification.

b) Clarification would enhance consistency

To prevent these inconsistencies in treatment, we believe that FDA should clarify how kits and virtual combination products should be treated with respect to submission of applications and designation of lead agency components. In addition, we encourage FDA to undertake improvements in the process to allow for maximum flexibility, while ensuring review by those agency components with the greatest expertise in the safety and effectiveness issues raised by a combination's constituent technologies. Specifically, we recommend that FDA:

- Allow submission of either combined or separate applications for constituent technologies of kits and virtual combination products, at the manufacturer's discretion. Clarify that combination products will be subject to one user fee, regardless of whether separate applications are filed.

- Designate appropriate lead agency components only when the manufacturer submits a combined application, or the manufacturer and

FDA agree that a coordinated review between agency components is necessary.

- Clarify that, once a lead agency component is appointed, applications submitted for constituent technologies will be subject to review by, or in coordination with, other relevant agency components, as provided in the Inter-center Agreements. This may mean separate reviews.

- Include in the preamble to the rule examples of how this approach might work in practice.

We believe this approach, which very closely parallels existing practice, fits within the existing law. As you well know, the statute requires FDA to determine the primary mode of action for each combination product and to designate the agency component with primary jurisdiction (the "lead agency component").[3] And as already observed, FDA has defined combination products to include both kits and virtual combination products.[4] However, 21 CFR § 3.4(b) specifically allows separate or "parallel" reviews of constituent technologies of a combination product. Indeed, this approach gives FDA maximum flexibility in reviewing kits and virtual combination products, while ensuring that the agency component with the greatest experience and expertise reviews each of the combination product's constituent technologies.

B. Primary Mode of Action/Algorithm

Overall, the CPC believes that the FDA's approach to primary mode of action faithfully implements the statute. In addition, we generally support FDA's use of an algorithm that provides a pathway for making more difficult determinations and adds consistency and transparency to the process. We are particularly pleased with a path that ensures assignment of combination products to the agency component that has experience with regulating combination products that present similar questions of safety and effectiveness, or if none exists, the agency component with the most expertise related to the most significant safety and effectiveness issues. Assignment to the agency component with the most experience or expertise is critical to ensuring protection of the public health as medical technology advances.

Despite our general support of the algorithm, we believe that the algorithm can be enhanced so that it better accommodates combination products that raise truly novel issues. However, before we offer our thoughts regarding how novel issues might be addressed within the steps of the algorithm, we have a preliminary question.

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[3] 21 U.S.C. 353(g)(1).

[4] *See* 21 CFR 3.2(e).

There has always been, in our minds at least, an ambiguity over what the agency means by the phrase "designation of agency component." On the one hand, part 3 can be read as describing a process for deciding which center will take the lead in the review process, and nothing more. On the other hand, the regulations incorporate by reference the inter-center agreements, and in section VII of those agreements, entitled "Center Jurisdiction", FDA describes how it will decide not just which center takes the lead in the review process, but which authorities under the statute will apply to that review process, which investigational options will be available, whether there are special labeling considerations that will apply, and whether inter-center consultations will be required. In practice, in some cases FDA also addresses such matters as post market reporting obligations and which GMPs apply. So our question is: what does FDA consider to be the designation of agency component controlled under this rule? Is it just the center designation, or does it include resolution of these additional issues? Knowing the answer to that is critical to commenting on this regulation, as we explain in each of the next three subsections.

With that question on the table, we turn to the issue of how novel features of combination products are treated at each of the three levels of analysis under the proposed algorithm.

1. Which mode of action provides the most important therapeutic action of the combination product?

For combination products for which the primary mode of action is certain, under the proposed rule FDA would not consider how to handle any particularly novel issues raised by the combination product at the time of designation. The focus at this first level of the algorithm is solely on the most important therapeutic action of a combination product, defined as the mode of action "expected to make the greatest contribution to the overall therapeutic effects of the combination products." While this focus makes sense and is consistent with the statute, it could result in assignment to an agency component that does not have the experience or expertise to handle the truly novel issues raised by a particular product. For instance:

- In a combination that includes a drug component and an *in vitro* diagnostic device component, the drug mode of action in most cases will be considered the most important because it provides the greatest contribution to the overall therapeutic effect of the combination product. Therefore, almost by default, a drug/IVD combination product will be assigned to the agency component for drugs. In many cases, however, it may be the IVD device that raises the most novel issues and associated questions of safety and effectiveness. As a result, the agency component

with the greatest expertise in addressing novel issues with IVD devices may not be the lead. Consequently, public health could be placed at risk.

- Similarly, a combination might include an already-approved drug component and a novel drug-delivery device where the drug mode of action may be considered the most important because it provides the greatest contribution to the overall therapeutic effect of the combination product. However, the novelty of such a combination product resides within the device component. For that reason, CDRH should take the lead. Consider an example in which the drug is insulin and the device is a novel insulin pump that administers the insulin subcutaneously. In this example, insulin itself, and the administration of insulin subcutaneously, are very well characterized and understood by the agency. There is no novelty in the drug component. However, the new insulin pump must be reviewed for its safety and efficacy. Because CDRH has the greatest expertise to review the novel issues raised by the drug delivery device, it makes sense that CDRH should be the lead center.

While we recognize that, despite their novel issues, these products must still be assigned to an agency component based on the PMOA, here are two instances in which our question about the scope of the designation is quite important.

If this rule is only meant to designate the lead center and nothing more, then perhaps nothing more needs to be said in this document, and our comment is more appropriate somewhere else. But in case the center designation process also controls the determination of the controlling authorities and the degree of collaboration between centers, then the rule needs to address how those decisions will be made for scenarios such as the examples presented above.

In that regard, we believe it is particularly important for FDA to tap into its statutory authority to use the most appropriate statutory authorities and human resources necessary to ensure an informed review of the safety and effectiveness of these products, including their novel attributes (i.e. the IVD and the insulin pump).[5] In such cases, FDA will need to facilitate close coordination or consultation between agency components to ensure that adequate review of novel issues occurs. In our examples above, the IVD and insulin pump need to be reviewed by people at CDRH and under the device authorities, even though the whole product has a drug PMOA. We think these are classic examples of where two submissions, separately reviewed, makes the most sense, even if CDER has the lead.

[5] *See* 21 USC 353(g)(2).

To avoid getting into too much detail in the regulation, FDA should consider preparing a guidance document describing how technologies that raise novel issues outside their PMOA should be reviewed from a procedural standpoint, and provide specific examples of the appropriate process.

2. Is there an agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole?

While we support this as the next level of the algorithm, it does have a weakness. The focus at this step of the algorithm is on similarity of experience. As a result, as with the prior step there is little opportunity for consideration of novel issues raised by a combination product that relate to the component that does not provide the most important therapeutic action. As discussed above, if this rule is meant to go beyond merely identifying the lead center and to address the designation of authorities and the interaction between centers, we believe FDA must consider those novel issues when making those other decisions.

Of course, when those novel issues rise to a level where they significantly affect safety and effectiveness, almost by definition this step in the algorithm is inapplicable and would be bypassed. If a product raises novel questions that could significantly impact safety and effectiveness, by definition there is no precedent to control the designation.

However, we note that the algorithm calls for the decision to be made with regard to the combination product as a whole. We are not really sure what that means. Say a company develops a contact lens that deploys a drug to treat macular degeneration. The agency has previously assigned a new contact lens that deploys a drug to treat glaucoma to CDER. (You might notice this example came from the proposed rule preamble.) Based on that precedent, we believe that agency would assign the contact lens/macular degeneration product to CDER, and that makes sense.

However, what happens if you flip the novel aspects? A company comes up with a truly different design for an intraocular lens ("IOL") -- for example, the IOL is deformable, allowing a variable focal length (such a design would require new materials, and in all likelihood, new ophthalmic surgical techniques for implantation.) The company wants to marry this IOL with a glaucoma drug, such that it delivers pilocarpine to the aqueous humor. Would the combination go to CDER because a glaucoma drug delivery system is associated with the new lens? Would the IOL go to CDER based on precedent, since ocular devices delivering glaucoma drug have traditionally gone to CDER? In our opinion, FDA needs the flexibility to determine that the prior decision is not precedent because the truly novel design of the IOL makes it a new product. In that

case, the agency would go to the next level of the algorithm. At a minimum, in cases like this, if FDA feels compelled to send it to CDER based on precedent, the agency needs to designate up front that the IOL will be reviewed through consultation with CDRH and under device authorities.

3. Which agency component has the most expertise related to the most significant safety and effectiveness questions presented by the combination product?

This point in the algorithm is perhaps the clearest point at which novel features can be considered in designating the lead agency component. Although, as discussed above, an agency component may not have the experience in analyzing similar safety and effectiveness questions when presented with a particularly novel issue, in all likelihood, one agency component will have expertise "related to" the significant new issues raised by a combination product. And we agree that is the agency component that makes the most sense to have reviewing the product.

We believe that an approach that considers the novelty of the constituent technologies in a combination product at the point of designating a lead agency will better ensure review by the agency components with the greatest expertise in the issues with perhaps the highest level of new risk. For that reason, we encourage FDA to consider these recommendations.

III. Conclusion

While we strongly support the FDA's efforts in clarifying and codifying the process for determining assignment of combination products, and believe that the Proposed Rule represents a significant, positive step, we believe that any rule that FDA promulgates must take into account the rapid innovation occurring in the combination products arena and the tremendous diversity and novelty of combination products likely to be submitted to the agency in the near future. For that reason, we recommend that FDA consider the potential enhancements presented here.

We appreciate the opportunity to present our comments on this important issue.

Respectfully submitted,

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for the Combination Products Coalition

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